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Antidepressants: misnamed and misrepresented

JOANNA MONCRIEFF

Department of Mental Health Sciences, University College London, London, UK

Modern evidence reveals that there is little difference between antidepressants and placebo for the treatment of depression. This is the message of Khan and Brown's review (1) of antidepressant research. In fact, older studies came to the same conclusion. In 1969, the authors of a comprehensive review commissioned by the U.S. National Institute of Mental Health concluded that "in well-designed studies, the differences between the effectiveness of antidepressant drugs and placebo are not impressive" (2, p. 19).

Problems with the evidence for antidepressants go even deeper than Khan and Brown suggest, however. Not only does this evidence show that these drugs are little different from placebo, but also that there are no grounds to believe they have specific effects that would justify their classification as "antidepressants".

Like other drugs used for mental health problems, drugs classed as antidepressants are psychoactive substances. Psychoactive substances are drugs that enter the brain and by doing so modify normal thoughts, emotions and behaviours. Recreational drugs have psychoactive properties that some people find pleasant or exciting, but other drugs – including antipsychotics, anti-convulsants and antidepressants – have psychoactive effects that are less appealing. The psychoactive effects of in-

dividual antidepressants vary in strength and character, with the effects of some, such as the selective serotonin reuptake inhibitors (SSRIs), being weak and subtle, whereas the effects of others are more profound (e.g., the tricyclics).

The fact that antidepressants are psychoactive substances has major implications for the interpretation of placebo-controlled trials. Firstly, the use of a psychoactive substance will inevitably impact on the experiences and emotions captured by depression rating scales. The sedative effects of antidepressants, such as the tricyclics and newer drugs like mirtazapine, for example, are likely to reduce the degree of agitation, anxiety and insomnia experienced by people with depression. These symptoms feature strongly in measurement scales. Changes in sleep alone can account for up to 6 points on the Hamilton Rating Scale for Depression, for example, whereas typical antidepressant-placebo differences are around 2 to 3 points (3,4). Moreover, psychoactive effects may impact in varied ways on thoughts.

Secondly, the psychoactive effects of antidepressants, along with the physical modifications they produce (both commonly referred to as "side effects", although this is misleading since an independent, therapeutic effect has not been established), will infringe the double blind design. Some of the participants allocated to the active drug will be able to detect that they have received the real drug because of the physical or mental changes the drug

produces, especially since they are provided with detailed information on possible side effects. Thus, it has been shown in many placebo-controlled trials of drugs used for mental health problems that participants can guess what they have received better than chance (5). In this situation, people allocated to the active drug are likely to have enhanced expectations of the effectiveness of therapy, and people who suspect they are taking placebo may have unduly negative expectations. Both of these factors may create or exaggerate a difference between antidepressants and placebo.

Unless the psychoactive effects of antidepressants are somehow discounted, differences between antidepressants and placebo cannot be interpreted as providing evidence that those drugs have a specific "antidepressant" effect. Indeed, it transpires that most drugs with psychoactive effects – including many antipsychotics, benzodiazepines, stimulants, buspirone and opiates (6) – produce the same changes as so-called antidepressants in randomized trials in people diagnosed with depression. Moreover, antidepressants themselves come from a wide array of chemical classes, and produce diverse pharmacological effects. Unsurprisingly, it seems that the experience of taking some sort of mind-altering substance produces a slightly different result from taking an inert placebo, when you attempt to measure people's thoughts and feelings (7,8).

If we accept this model, we need to ask whether the psychoactive effects

that antidepressants or other drugs produce might logically be useful in people with depression. There may, for example, be a role for temporary use of drugs with sedative properties to manage insomnia, anxiety and agitation in people who experience these symptoms, balancing proper evidence of benefits against adverse effects, including risks of dependence.

There has been some debate as to whether the SSRIs and related antidepressants produce a state of emotional suppression or disengagement. Antipsychotics are well known for dulling emotions, but the effects of SSRIs are likely to be more subtle. Evidence from converging sources now suggests that SSRIs and other newer antidepressants do have this property, and that it is associated with recognized side effects, such as loss of libido and sexual impairment (9-11). Many people dislike this state of emotional numbing but, in theory, some may find it useful to manage an intense emotional crisis. Again, we need evidence to explore whether this particular effect produces any tangible improvement in people suffering from depression, and whether people find it acceptable or not.

For decades now people have been told that depression is a chemical imbalance and that antidepressants work by correcting that imbalance. This view is not supported by evidence, and is misleading as to the nature and effects of antidepressant drugs. We need to recognize that antidepressants are psychoactive substances, we need more data on the nature of the varied psychoactive effects they produce, and we need to explore whether giving drugs that produce an artificially altered emotional state is a useful and acceptable intervention for people with depression.

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Antidepressant or antidepressant plus placebo effect?

STUART A. MONTGOMERY

Imperial College School of Medicine, University of London, London, UK

Since the first observations of the therapeutic effect of imipramine, an extensive armamentarium of effective antidepressant medications has been developed, but the level of efficacy achieved appears to be considerably less today than might have been predicted from the discoveries of more than 40 years ago. Public opinion is currently suspicious as to the value of antidepressants in treating depressive illness. Khan and Brown's (1) thoughtful elucidation of possible factors involved helps to clarify if there has been a change in the way studies to establish

efficacy are conducted, a change in the patients coming forward for treatment, and whether we should change our expectations on treatment efficacy.

The rise in the response to placebo reported in clinical studies, which certainly makes the demonstration of efficacy more difficult, has been attributed by some to pressure from the pharmaceutical industry to find a rewarding outcome in efficacy studies. The comparison of Khan et al (2) of the symptom reduction data reported in non-pharmaceutical industry studies with the data submitted by pharmaceutical companies to the U.S. Food and Drug Administration (FDA) finds few substantive differences. Differences in assessments between the two data-

sets appear to be related to size rather than direction, and when the non-pharmaceutical investigators were unaware of the study design the assessments came even closer to those of the FDA data. Industry-sponsored studies submitted for regulatory approval are designed in discussion with the regulatory authorities and have to meet their strict criteria; the similarity of the data from the two sources is reassuring.

Clinicians recognize the powerful contribution of placebo response in depression as in many other conditions. The task of distinguishing the pharmacological from the placebo response has become more difficult over the years, as the proliferation in regulatory requirements to address